DOCKET NO.: 133088.00701 (P37166US) **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: **Owen Smith**

Title: **Diagnosis Of Pre-Eclampsia**

Serial No.: **10/560,954**

Filed: **October 9, 2006**

Group Art Unit: **1657**

Examiner: **Tiffany Maureen Gough**

Confirmation No.: **1704**

Filed via EFS-Web on: **4 February 2010**

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pre-Appeal Brief Request for Review

In response to the Final Rejection dated August 31, 2009 and the Advisory Action dated December 24, 2009, Applicant respectfully requests reconsideration of the pending rejections.

I. Claims 1 and 3-5 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the combination of: 1) WO 00/08207; 2) U.S. Patent No. 6,753,159; 3) Fossati et al., Clin. Chem., 1980, 26, 227-231; 4) Owen-Smith et al., The Lancet, 1998, 1, 1 (hereinafter, the "Owen-Smith I reference"); and 5) Owen-Smith et al., Salivary Urate as an Indicator of Metabolic Stress, (hereinafter, the "Owen-Smith X reference"); in further view of each of a) Dunlop et al., Brit. Med. J., 1978, b) Schuster et al., Gynecol. Obstet., 1981, 12, abstract, and c) Pipkin et al., J. Hypertension, 2004, 22, 237-239 (hereinafter, the "Pipkin reference").

A. The Office has clearly erred by considering the Owen-Smith X reference prior art.

The Office has based its obviousness rejection on the Owen-Smith X reference, in which it is stated, "Non-invasive monitoring of salivary urate may help in the management of pre-eclampsia." However, this document, as explained in detail in the response to the office action filed on 28 October 2009 **was not published and was never made publically available**. The reason the Office even has a copy of this document is because it was sent to the Office by the Applicant on 15 April 2009 in support of an argument that using salivary urate to diagnose preeclampsia is **not obvious**. It was explained in the submissions of 15 April 2009 that the draft was **not a public document**. The Office, however, has now **arbitrarily assigned** a publication year of 1981 and cited that document against the Applicant. It is apparent, then, that the Owen-Smith X reference is **not prior art** and **cannot be used by the Office to support a rejection under 35 U.S.C. §103(a).**

The Owen-Smith X reference is an unpublished draft of a paper that was later published in a modified form and without reference to uric acid in preeclampsia in the Lancet and is now cited as the Owen-Smith I reference. In 1997, the Owen-Smith X reference was sent by the inventor (Dr. Brian Owen-Smith) to a consultant obstetrician Mr. Jonathan Hooker at St. Richard Hospital in Chichester, UK, for his opinion on a possible link between salivary urate and preeclampsia.

B. The Office has clearly erred by ignoring the Owen-Smith X reference content in view of the Declaration of Mr. Hooker.

As a consultant obstetrician (equivalent to an attending physician), Mr. Hooker regularly deals with patients with preeclampsia. Obstetrics is the surgical branch of medicine related to the care of women and their children during pregnancy and childbirth, as well as postnatal care. Mr. Hooker is therefore involved in the diagnosis and management of such patients and has a good understanding of the condition from the perspective of an obstetrician. Therefore, he could be considered a person of ***exceptional*** skill in the art. However, on reviewing Dr. Owen-Smith's findings, Mr. Hooker concluded that there was **no significant link between salivary urate and preeclampsia**. Instead, Mr. Hooker believed that blood urate in preeclampsia is more to do with impaired renal function, and provided references in support.

This was evidenced in the response filed on 15 April 2009 with a copy of the letter sent from Mr. Hooker to the inventor Dr. Owen-Smith in 1997. Moreover, a signed Declaration by Mr. Hooker was also submitted. This is clear and unambiguous evidence that at the time of filing the application, the concept of using salivary urate to diagnose preeclampsia was **not obvious** at the priority date, **even to a person of *exceptional* skill in the art of obstetrics**.

C. The Office has clearly erred by ignoring evidence provided by Applicant.

Applicant has also submitted further extensive evidence supporting the argument that an obstetrician (a person of skill in the relevant art) would not consider salivary urate to be relevant to the diagnosis as set out in detail, for example, in the responses filed on 15 April 2009 and 28 October 2009, which is briefly summarized below.

In times of oxidative stress (for example during exercise), purine metabolism increases and hence the level of urate in the body increases. See, for example, Owen-Smith reference I (cited by the Examiner). This document teaches that at times of oxidative stress such as exercise, levels of urate in the saliva can be used to measure changes *in purine metabolism.*

The present application works on the hypothesis that, as a result of placental dysfunction, a pre-eclamptic mother and fetus are placed under oxidative or metabolic stress. This causes increased purine degradation and as a result increased production of uric acid. Fetal

production of uric acid is increased and excreted into both the amniotic and maternal extracellular fluid compartments and subsequently into intestinal secretions and saliva. In addition, oxidative stress also affects the kidneys and causes reduced urine uric acid excretion. The combination of renal retention and increased salivary urate excretion is the mechanism which causes daily variation (increased salivary urate concentration in the morning) thereby considerably **increasing the sensitivity of the claimed saliva test as compared with blood urate**. Therefore, the present application proposes **for the first time** to use salivary urate as an indicator of purine metabolism in pregnant women as a diagnostic test of pre-eclampsia and fetal well-being.

In contrast, the art of obstetrics teaches that diagnosis of pre-eclampsia is based on hypertension, in association with protein in the urine and oedema. See, for example, "The management of severe pre-eclampsia/eclampsia" published by the Royal College of Obstetricians and Gynaecologists in March 2006 (submitted previously), where it states:

> "Pre-eclampsia is pregnancy-induced hypertension in association with proteinuria (>0.3 g in 24 hours) ± oedema and virtually any organ system may be affected" (see page 1, third paragraph).

Furthermore, obstetricians consider the main factor controlling blood plasma urate levels in pre-eclamptic women as being the result of changes in renal excretion. See, for example, the extract from "Medical Disorders of Pregnancy" by de Swiet (1989) submitted to the USPTO previously:

> "Normal pregnancy induces relative hypouricaemia. Plasma* urate concentrations decrease by over 25 per cent as early as week 8 of pregnancy, but increase again during the third trimester to attain levels close to the non-pregnant mean. **The main reason for this is alteration in the renal handling of urate** which, although freely filtered, is subsequently so actively re-absorbed that only about 10 per cent of the original filtered load appears in the urine. Later in pregnancy the kidney appears to excrete an even smaller proportion of filtered urate load and it is this increase in net reabsorption that is associated with an increase in plasma urate concentration" (see page 231, column 1, paragraph 2, emphasis added).

Nowhere in the obstetric art is it taught that one third of urate is eliminated in the gut via saliva and intestinal secretions. The above extract also demonstrates there is a poor understanding of the mechanisms surrounding purine metabolism and the effect of oxidative stress on the levels of urate in the body.

It is clear, therefore, that **the inventor worked contrary to accepted principles in obstetrics and in a non-obvious manner** to achieve the claimed invention. The fact that it was known that urate can be found in extracellular fluid such as blood plasma and saliva is not relevant, for the following reasons.

Firstly, the link between urate and preeclampsia was not a universally accepted one at the priority date and there were many contradictions in the art, including in the very documents cited by the Examiner (explained in detail in the previous submissions. *See*, for example, Pipkin reference, page 238, column 2, paragraph 3, lines 8 to 10 where it is stated "one prospective study from first trimester pregnancy **urate production was actually lower in women who went on to develop pre-eclampsia**", emphasis added).

Secondly, much of the art relating to urate levels in the body are concerned with plasma urate levels. In contrast, the fetus is contained in amniotic fluid, which is derived from extracellular fluid and fetal urine and is distinct and separate in physiological terms from the blood plasma. Saliva is also secreted from extracellular fluid. Applicant has already submitted considerable evidence proving that this is the case. Even if an obstetrician wanted to measure the levels of urate in a pregnant mother (for assessment of renal function or diagnosis of preeclampsia) they would measure the levels of urate in the blood plasma and **not** in the saliva as they would understand these to be separate compartments of the extracellular fluid. **It is the non-obvious link between salivary urate and preeclampsia that forms one basis of the claimed invention and which demonstrates the true inventive nature of the application**.

Despite having provided considerable evidence that a person of skill in the art would not consider measuring salivary urate to diagnose preeclampsia, this extensive argumentation appears to have been **ignored** by the Office. The Advisory Action simply states that the arguments were "not persuasive", without providing any reasons. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. §103(a) be withdrawn.

II. Claims 1 and 3-5 are also rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as his invention.

A. The Office has clearly erred by ignoring the specification.

The Office asserts that "it is not clear how the sample is processed or assayed as there are no actual processing and assaying steps claimed" (see, Final Rejection at page 2). Applicant respectfully points out that the description of the invention is the role of the specification, not the claims. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ.2d 1081 (Fed. Cir. 1986). The specification contains examples of "processing" a sample of maternal saliva collected from a subject prior to assaying (see, for example, paragraph 0016 which teaches that the collected sample of saliva is transported and processed by a laboratory where the tube may be centrifuged so that it is ready for assay; paragraph 0037 which teaches that upon collection of saliva, a swab containing the saliva is returned to the insert in the Salivette®, which is appropriately labeled, and kept cool in a refrigerator until it is transported and processed by the laboratory; paragraph 0038 which teaches that upon receipt at the laboratory and after laboratory and patient information is collected from the tube label, the Salivette® tube with the swab insert is centrifuged which results in a clear sample of mixed saliva that is ready for assay). Thus, the specification amply teaches one skilled in the art "processing" of the collected sample. In addition, the specification is replete with examples of assaying the sample for the concentration of urate present (see, for example, paragraph 0017 which teaches that levels of urate in the biological sample can be measured by any suitable test or biological assay, including a dip stick test, the timed end point method, or the dry test method, each of which are further explained in paragraphs 0018-0021). Thus, there can be no question that Applicant provides ample description in the specification of assaying the sample for the concentration of urate present. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

Applicant respectfully submits that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Office is invited to contact Applicant's undersigned representative at 610.640.7859 to resolve any remaining issues.

The Commissioner is hereby authorized to debit any underpayment of fee due or credit any overpayment to Deposit Account No. 50-0436.

Respectfully submitted,

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Date: **4 February 2010**

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